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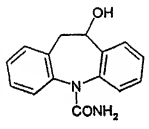
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MONOHYDROXYCARBAMAZEPINE FOR USE IN THE PREPARATION OF A MEDICAMENT FOR THE TREATMENT OF AFFECTIVE AND ATTENTION DISORDER AND NEUROPATHIC PAIN



(I)

(57) Abstract: The invention relates to the use of a carbamazepine derivative of the Formula (I) for the treatment of affective and attention disorders, neuropathic pain and neuropathic pain related disorders.

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in (bipolar) mood disorders and also in anxiety and depression, e.g. lithium, valproate and diazepam are known to inhibit the GABA turnover rate. This is due to feedback inhibition caused by the activating effect of these compounds on GABA transmission.

Also, the role of GABA in chronic pain is unquestioned and topic of several reviews (e.g., Stamford. Descending control of pain. Br. J. Anaesth. 1995; 75:217-21). Drugs effective in chronic pain such as valproate are known to inhibit the GABA turnover rate. This is due to feedback inhibition caused by the activating effect of these compounds on GABA transmission.

The activity of the compound of formula I on GABA turnover is evidenced in the following experiment:

The determination of GABA turnover is based on the linear increase in GABA level observed after the maximal inhibition of gamma- aminobutyric acid transaminase (GABA-T). The values obtained with this approach for the rate of GABA synthesis are independent of the inhibitors used and within the catalytic capacity of the enzymes involved in the GABA shunt.

Under these conditions, the compound of formula I dose-dependently inhibits the GABA turnover rate at doses of 30 to about 300 mg/kg p.o.

The activity of the compound of formula I in the treatment of affective and attention disorders treatment is also evidenced, for example, in tests suitable for detecting drugs having potential behavioural desinhibitory and/or sociotropic effects which are thought to be relevant for recovery from social withdrawal, a cardinal feature of depression and related psychiatric conditions. For instance, drug effects on social withdrawal of intruder mice can be evaluated by using the basic method as described in Triangle, 1982, 21:95-105 and J. Clin. Psychiatry, 1994, 55:9 (suppl. B) 4-7.

Within the dose range of 1 to about 100 mg/kg p.o., the compound of formula I increases social investigation in the treated mouse under such experimental conditions.

In view of its anxiolytic-/antidepressant- like stimulating effect on GABA transmission and sociotropic activity, the compound of formula I is useful in the treatment of affective disorders

pain, migraine, causalgia and deafferentation syndromes such as brachial plexus avulsion, and in spasticity and related disorders.

For the above-mentioned indications, the appropriate dosage will of course vary depending upon, for example, the compound employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 0.05 to about 150, preferably from about 0.1 to about 100 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 0.5 to about 5000, preferably from about 1 to about 500mg of an agent of the invention, conveniently administered, for example, in divided doses up to four times a day or in sustained release form, for example once a day.

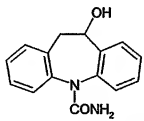
The agent of the invention may be administered by any conventional route, in particular enterally, preferably orally, for example in the form of tablets or capsules, or parenterally, for example in the form of injectable solutions or suspensions.

The agents of the invention can be administered in vivo either alone or in combination with other pharmaceutical agents, e.g. agents effective in the treatment of diseases and conditions in which the human VR1 activation plays a role or is implicated including cyclooxygenase-2 (COX-2) inhibitors, such as specific COX-2 inhibitors (e.g. celecoxib, COX189, and rofecoxib) or in general nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g. acetylsalicylic acid, propionic acid derivatives), tricyclic antidepressants (e.g. Anafranil®, Asendin®, Aventyl®, Elavil®, Endep®, Norfranil®, Norpramin®, Pamelor®, Sinequan®, Surmontil®, Tipramine®, Tofranil®, Vivactil®, Tofranil-PM®), anticonvulsants (e.g. gabapentin), $GABA_B$ agonists (e.g. L-baclofen), opioids, Vanniloid receptor antagonists and Cannabinoid (CB) receptor agonists, e.g. CB_1 receptor agonists.

The pharmaceutical compositions for separate administration of the combination partners and for the administration in a fixed combination, i.e. a single galenical composition comprising at least two combination partners, according to the invention can be prepared in a manner known per se and are thus suitable for enteral, such as oral or rectal, and parenteral administration to mammals, including man, comprising a therapeutically effective amount of at least one pharmacologically active combination partner alone or in combination

Claims:

1. The use of monohydroxycarbamazepine of formula I



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for the treatment of affective and attention disorders, neuropathic pain and neurophatic pain related disorders.

2. A pharmaceutical composition comprising the compound of formula I according toclaim 1, in association with at least one pharmaceutical carrier or diluent, for use in the treatment of affective and attention disorders, neurophatic pain and neurophatic pain related disorders.

3. The use of the compound of formula I according to claim 1, for the manufacture of a pharmaceutical composition for the treatment of affective and attention disorders, neurophatic pain and neurophatic pain related disorders.

4. A method for the treatment of affective and attention disorders, neurophatic pain and neurophatic pain related disorders in a subject in need of such treatment, which comprises administering to said subject a therapeutically effective amount of the compound of formula I according to claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/12578

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1,4 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.